ROCK Inhibition Extends Passage of Pluripotent Stem Cell-Derived Retinal Pigmented Epithelium.

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Public Summary:
Human embryonic stem cells (hESCs) offer a potentially unlimited supply of cells for emerging cell-based therapies. Unfortunately, the process of deriving distinct cell types can be time consuming and expensive. In the developed world, age-related macular degeneration (AMD) is the leading cause of blindness in the elderly, with more than 7.2 million people afflicted in the U.S. alone. Both hESC-derived retinal pigmented epithelium (hESC-RPE) and induced pluripotent stem cell-derived RPE (iPSC-RPE) are being developed for AMD therapies by multiple groups, but their potential for expansion in culture is limited. To attempt to overcome this passage limitation, we examined the involvement of Rho-associated, coiled-coil protein kinase (ROCK) in hESC-RPE and iPSC-RPE culture. We report that inhibiting ROCK1/2 with a small molecule inhibitor allows extended passage of hESC-RPE and iPSC-RPE. This finding is significant in that it removes a bottleneck in the production of this potentially useful cell type. It is now possible to grow large amounts of cells that have shown promise in treating age-related macular degeneration.

Scientific Abstract:
Human embryonic stem cells (hESCs) offer a potentially unlimited supply of cells for emerging cell-based therapies. Unfortunately, the process of deriving distinct cell types can be time consuming and expensive. In the developed world, age-related macular degeneration (AMD) is the leading cause of blindness in the elderly, with more than 7.2 million people afflicted in the U.S. alone. Both hESC-derived retinal pigmented epithelium (hESC-RPE) and induced pluripotent stem cell-derived RPE (iPSC-RPE) are being developed for AMD therapies by multiple groups, but their potential for expansion in culture is limited. To attempt to overcome this passage limitation, we examined the involvement of Rho-associated, coiled-coil protein kinase (ROCK) in hESC-RPE and iPSC-RPE culture. We report that inhibiting ROCK1/2 with Y-27632 allows extended passage of hESC-RPE and iPSC-RPE. Microarray analysis suggests that ROCK inhibition could be suppressing an epithelial-to-mesenchymal transition through various pathways. These include inhibition of key ligands of the transforming growth factor-beta pathway (TGFB1 and GDF6) and Wnt signaling. Two important processes are affected, allowing for an increase in hESC-RPE expansion. First, ROCK inhibition promotes proliferation by inducing multiple components that are involved in cell cycle progression. Second, ROCK inhibition affects many pathways that could be converging to suppress RPE-to-mesenchymal transition. This allows hESC-RPE to remain functional for an extended but finite period in culture.